

REMARKS/ARGUMENTS.

Claim 1 has been amended to limit to imaging moieties which are radioactive. Claim 1 has also been amended to specify that the imaging agent is “a PET or SPECT *in vivo* imaging agent”. Basis can be found at page 5, lines 26-29 of the specification. Claim 5 has consequently been withdrawn. The subject matter of claims 10, 12 and 13 has been cognated into revised claim 1. With regard to claims 11 and 13, although those claims were previously withdrawn, claim 5 at (i) and (iv) refers to the same subject matter in broader terms, hence that subject matter was still under examination but now claim 5 has been withdrawn.

Dependent claims 8, 19 and 22 have been amended to ensure consistency with the essential features of revised claim 1. Claims 3, 5, 7, 10-15, 18, 32, and 34-36 remain or have been withdrawn. The pending claims are now: 1, 2, 4, 6, 8-9, 16-17, 19-31 and 33.

1. 35 USC §103 (Obviousness) Rejections.

All the previous claims under consideration (1-2, 4-6, 8-10, 12, 16-31 and 33) continue to be rejected as being obvious over the combination of either Carpenter *et al* (WO 01/60416) or Mobashery (WO 01/92244) in view of Sahagan (EP 1088550 A1).

The Examiner argues that the phraseology of previous claim 1 “suitable for diagnostic imaging *in vivo* is allegedly an intended use, and as such does not preclude prior art agents capable of performing the intended use.

Applicants stress that revised claim 1 is now limited to a PET or SPECT *in vivo* imaging agent. The ‘imaging moiety’ is now limited to the radioisotopes defined in (i)-(iii) of revised claim 1.

Revised claim 1 requires that the agent is a PET or SPECT *in vivo* imaging agent. Specific radioisotopes are cited at (i) – (iii) as essential features. Hence, it is no longer the case that any prior art deemed “capable” would be relevant – the prior art must teach the combination of essential features of revised claim 1. It is well settled in the law that a reference must be considered not just for what it expressly teaches, but also for what it fairly suggests to one who is unaware of the claimed invention. *In re Baird*, 16 F.3d 380, (Fed. Cir. 1994).

In the Examiner’s response to applicant’s previous arguments (page 15 line 6 to page 19 line 17), the Examiner does not address applicant’s key arguments about the fact that present claim 1 requires that the imaging moiety is attached only at Y¹ or Y². Reference was made to the rejection of the Office Action dated 07/08/2008, but that does not specifically address the ‘site of attachment’ issue. It as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art. *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443 (Fed. Cir. 1986). (emphasis added).

Sahagan, at [0043] page 10 lines 34 to 40 discloses only ³H and ¹⁴C as suitable radioisotopes for “drug and/or substrate tissue distribution assays”. Those radioisotopes are outside the scope of present claim 1. It is well settled in the law that a reference must be considered not

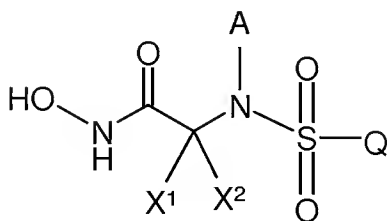
just for what it expressly teaches, but also for what it fairly suggests to one who is unaware of the claimed invention. *In re Baird*, 16 F.3d 380, (Fed. Cir. 1994).

The Examiner suggests that it would be obvious to combine the imaging labels of Carpenter or Mobashery with the MMP inhibitors taught by Sahagan. Applicants respectfully disagree as set forth.

Carpenter/Mobashery/Sahagan combination.

Applicants disagree that the motivation to combine exists (see arguments filed 07 April 2009), but even assuming that such motivation existed, the question remains of which element(s) of the teaching of Carpenter/Mobashery could be applied to Sahagan. The Examiner has already acknowledged that the MMPis of Carpenter are structurally dissimilar to those of the present invention – and hence also those of Sahagan.

The inhibitors of Sahagan are of Formula (I) of claim 1 therein:

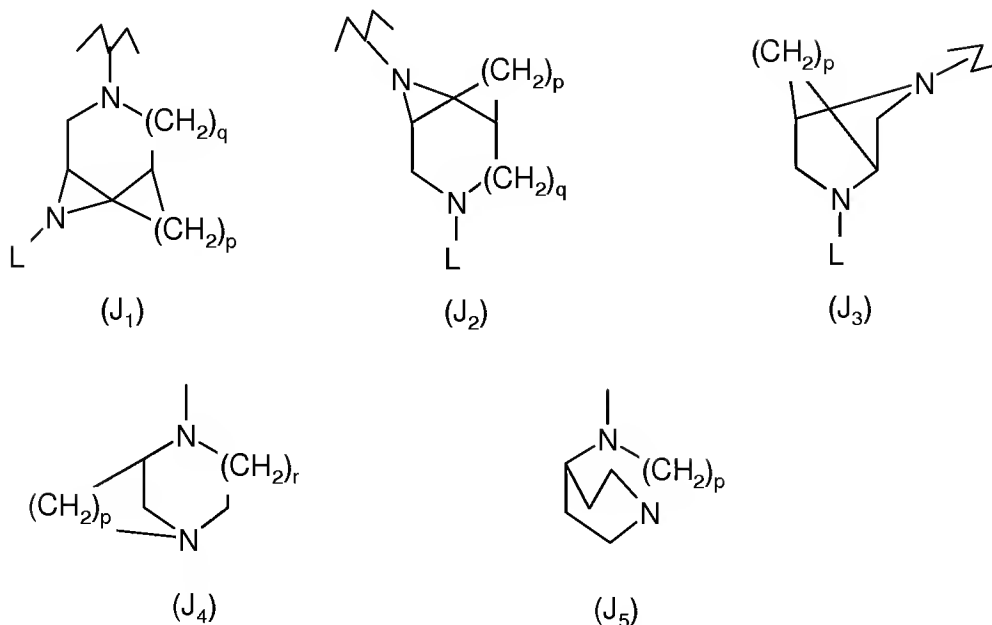


wherein

A is H or-(CH₂)_n-(C=O)-Z; where n is 1 to 6; and

Z is hydroxy, (C₁-C₆)alkoxy or NR¹R² wherein R¹ and R² are each independently selected from the group consisting of H, (C₁-C₆)alkyl, piperidyl, (C₁-C₆) alkylpiperidyl, (C₆-C₁₀)

arylpiperidyl, (C₂-C₉) heteroarylpiperidyl, (C₆-C₁₀) aryl(C₁-C₆)alkylpiperidyl, (C₂-C₉)heteroaryl(C₁-C₆)alkylpiperidyl, (C₁-C₆)acylpiperidyl, (C₆-C₁₀)aryl, (C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, R⁵(C₂-C₆)alkyl, (C₁-C₅)alkyl(CHR³)(C₁-C₆)alkyl wherein R³ is hydroxy, (C₁-C₆)acyloxy, (C₁-C₆)alkoxy, piperazino, (C₁-C₆)acylamino, (C₁-C₆)alkylthio, (C₆-C₁₀) arylthio, (C₁-C₆)alkylsulfinyl, (C₆-C₁₀)arylsulfinyl, (C₁-C₆)alkylsulfoxyl, (C₆-C₁₀)arylsulfoxyl, amino, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂ amino, (C₁-C₆)acylpiperazino, (C₁-C₆)alkylpiperazino, (C₆-C₁₀)aryl(C₁-C₆)alkylpiperazino, (C₂-C₉) heteroaryl(C₁-C₆)alkylpiperazino, morpholino, thiomorpholino, piperidino or pyrrolidino; R⁴(C₁-C₆)alkyl, (C₁-C₅)alkyl(CHR⁴)(C₁-C₆)alkyl wherein R⁴ is piperidyl, (C₁-C₆)alkylpiperidyl, (C₆-C₁₀) arylpiperidyl, (C₆-C₁₀)aryl(C₁-C₆)alkylpiperidyl, (C₂-C₉)heteroarylpiperidyl or (C₂-C₉)heteroaryl(C₁-C₆)alkylpiperidyl; and CH(R⁵)COR⁶ wherein R⁵ is hydrogen, (C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkyl, (C₁-C₆)alkylthio(C₁-C₆)alkyl, (C₆-C₁₀) arylthio(C₁-C₆)alkyl, (C₁-C₆)alkylsulfinyl(C₁-C₆)alkyl, (C₆-C₁₀)arylsulfinyl(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl(C₁-C₆)alkyl, (C₆-C₁₀)arylsulfonyl(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, ((C₁-C₆)alkylamino)₂ (C₁-C₆)alkyl, R⁷R⁸NCO(C₁-C₆)alkyl or R⁷OCO(C₁-C₆)alkyl wherein R⁷ and R⁸ are each independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₉)heteroaryl(C₁-C₆)alkyl; and R⁶ is or R⁹R¹⁰N wherein R⁹ and R¹⁰ are each independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₉)heteroaryl(C₁-C₆)alkyl; or R¹ and R², or R⁷ and R⁸, or R⁹ and R¹⁰ may be taken together to form an azetidiny, pyrrolidinyl, morpholinyl, thiomorpholinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, (C₁-C₆)acylpiperazinyl, (C₁-C₆)alkylpiperazinyl, (C₆-C₁₀)arylpiperazinyl, (C₂-C₉)heteroarylpiperazinyl or a bridged diazabicycloalkyl ring selected from the group consisting of:



wherein

p is 1, 2 or 3;

q is 1 or 2;

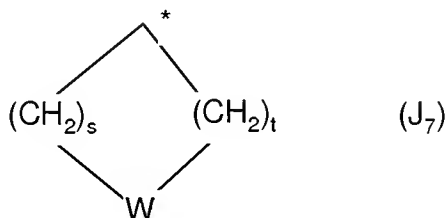
r is 0 or 1 ;

L is hydrogen, (C₁-C₃)alkyl or (C₁-C₆)acyl;

X¹ and X² are each independently selected from the group consisting of H, (C₁-C₆)alkyl, trifluoromethyl, trifluoromethyl(C₁-C₆)alkyl, (C₁-C₆)alkyl (difluoromethylene), (C₁-C₃)alkyl(difluoromethylene)(C₁-C₃)alkyl, (C₆-C₁₀)aryl, (C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₁-C₆)acyloxy(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, piperazinyl(C₁-C₆)alkyl, (C₁-C₆)acylamino(C₁-C₆)alkyl, piperidyl, (C₁-C₆)alkylpiperidyl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₁-C₆)alkylthio(C₁-C₆)alkyl, (C₆-C₁₀)arylthio(C₁-C₆)alkyl, (C₁-C₆)alkylsulfinyl(C₁-C₆)alkyl, (C₆-C₁₀)arylsulfinyl(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl(C₁-C₆)alkyl, (C₆-C₁₀)arylsulfonyl(C₁-C₆)alkyl, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, ((C₁-C₆)alkylamino)₂(C₁-C₆)alkyl, R¹¹CO(C₁-

C₆)alkyl wherein R¹¹ is R¹²O or R¹²R¹³N wherein R¹² and R¹³ are each independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl or (C₂-C₉)heteroaryl(C₁-C₆)alkyl; and R¹⁴(C₁-C₆)alkyl wherein R¹⁴ is (C₁-C₆)acylpiperazino, (C₆-C₁₀)arylpiperazino, (C₂-C₉)heteroarylpiperazino, (C₁-C₆)alkylpiperazino, (C₆-C₁₀)aryl(C₁-C₆)alkylpiperazino, (C₂-C₉)heteroaryl(C₁-C₆)alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, (C₁-C₆)alkylpiperidyl, (C₆-C₁₀)aryl(C₁-C₆)alkylpiperidyl, (C₂-C₉)heteroaryl(C₁-C₆)alkylpiperidyl, (C₆-C₁₀)aryl(C₁-C₆)alkylpiperidyl, (C₂-C₉)heteroaryl(C₁-C₆)alkylpiperidyl or (C₁-C₆)acylpiperidyl;

or X¹ and X² may be taken together to form a (C₃-C₆)cycloalkyl, a benzo-fused (C₃-C₆)cycloalkyl ring or a group of the formula (J₇):



wherein the carbon atom bearing the asterisk is the carbon to which X¹ and X² are attached, s and t are independently 1 or 2, and W is CF₂, O, S, SO₂ or NR¹⁵, wherein R¹⁵ is H, (C₁-C₆)alkyl, (C₆-C₁₀)acyl, (C₆-C₁₀)aryl, (C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl, (C₆-C₁₀)arylsulfonyl or (C₁-C₆)alkyl(C=O)-;

Q is (C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₂-C₉)heteroaryl, (C₆-C₁₀)aryloxy(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl(C₆-C₁₀)aryl, (C₁-C₆)alkyl(C₆-C₁₀)aryl, (C₁-C₆)alkoxy(C₆-C₁₀)aryl, ((C₁-C₆)alkoxy)₂(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₂-C₉)heteroaryloxy(C₆-C₁₀)aryl, (C₁-C₆)alkyl(C₂-C₉)heteroaryl, (C₁-C₆)alkoxy(C₂-C₉)heteroaryl, ((C₁-C₆)alkoxy)₂(C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryloxy(C₂-C₉)heteroaryl, (C₆-C₁₀)aryloxy(C₁-C₆)alkyl, (C₂-C₉)heteroaryloxy(C₁-C₆)alkyl, (C₁-C₆)alkyl(C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, (C₁-C₆)alkyl(C₂-C₉)heteroaryloxy(C₆-C₁₀)aryl, (C₁-C₆)alkyl(C₆-C₁₀)aryloxy(C₂-C₉)heteroaryl, (C₁-C₆)

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alkoxy(C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, (C₁-C₆)alkoxy(C₂-C₉)heteroaryloxy(C₆-C₁₀)aryl or (C₁-C₆)alkoxy(C₆-C₁₀)aryloxy(C₂-C₉)heteroaryl, wherein each of the foregoing aryl groups may be optionally substituted by fluoro, chloro, bromo, trifluoromethyl, trifluoromethoxy, difluoromethoxy, (C₁-C₆)alkyl, (C₁-C₆) alkoxy or perfluoro(C₁-C₃)alkyl;

with the proviso that when either X¹ or X² is CH(R⁵)COR⁶ wherein R⁵ and R⁶ are as defined above, the other of X¹ or X² is H, (C₁-C₆)alkyl or benzyl.

The range of substituents on the MMP inhibitors taught by Sahagan is thus vast in scope. Sahagan provides no teaching on the location of any radiolabel, except that it must be intrinsic to the chemical structure. The Examiner has argued that Carpenter and/or Mobashery can be combined with Sahagan. Even if such a combination were to be contemplated, there are inevitably a huge number of possible locations for the radioisotope. In view of the circumstances, applicants contend that choice of labeling at Y¹ or Y² of present Formula I cannot be derived in an obvious manner from Carpenter/Mobashery/Sahagan.

Sahagan itself is silent on sites of labeling. As acknowledged by the Examiner, Carpenter and Mobashery relate to chemically very different MMP. Mobashery also is silent on sites of labeling. The sites of labeling taught by Carpenter teach away from the subject matter of the present claims – see applicants response filed 07 April 2009.

Since none of Carpenter/Mobashery/Sahagan can provide the teaching of labeling at Y¹ and Y², present claim 1 is believed non-obvious over the combination

Carpenter/Mobashery/Sahagan. Accordingly, Applicants respectfully request that the Examiner withdraw the rejections for currently amended claims 1-2, 4, 6, 8-9, 16-17, 19-31 and 33 under 35 U.S.C. §103(a) and direct that those claims be allowed.

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6. Double Patenting.

Claims 1-2, 4-10, 13 and 16-31 are provisionally rejected under the doctrine of obvious-type double patenting, as being unpatentable over claims 1-21, 24-28, 30-31 and 35 of copending US patent application 10/544945. In response, Applicants submit that a terminal disclaimer will be filed once the instant application is indicated to be allowable.

CONCLUSION

Upon entry of this Amendment, claims 1, 2, 4, 6, 8-9, 16-17, 19-31 and 33 remain pending. Applicants submit that all outstanding issues have been addressed, and that claims 1, 2, 4, 6, 8-9, 16-17, 19-31 and 33 are in condition for allowance, which action is earnestly solicited.

The Commissioner is hereby authorized to charge any fees under 37 CFR §1.16(j) or 37 CFR 1.136(a) which may be required, or credit any overpayment, to Deposit Account No. 502-665 in the name of GE Healthcare, Inc.

Should any other matters require attention prior to allowance of the application, it is requested that the Examiner contact the undersigned.

Respectfully submitted,

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